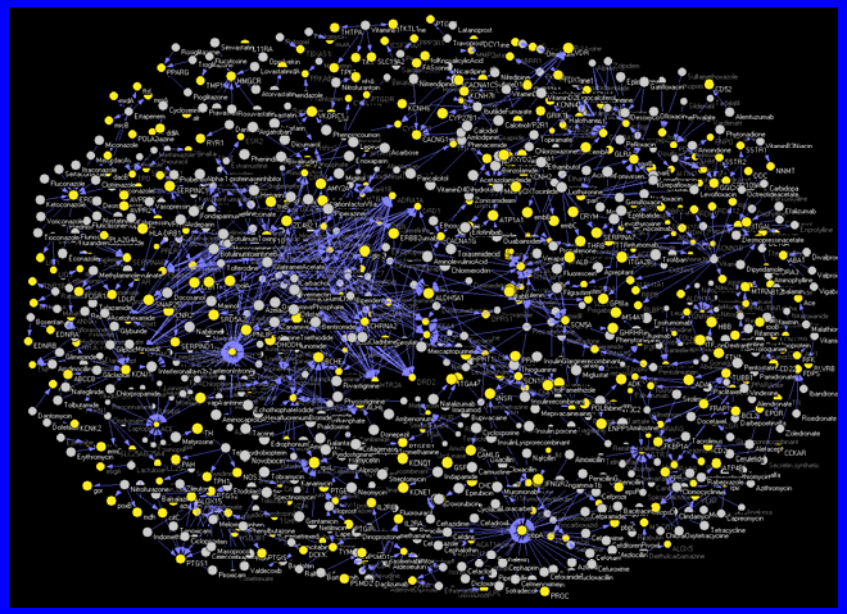

Systems Pharmacology

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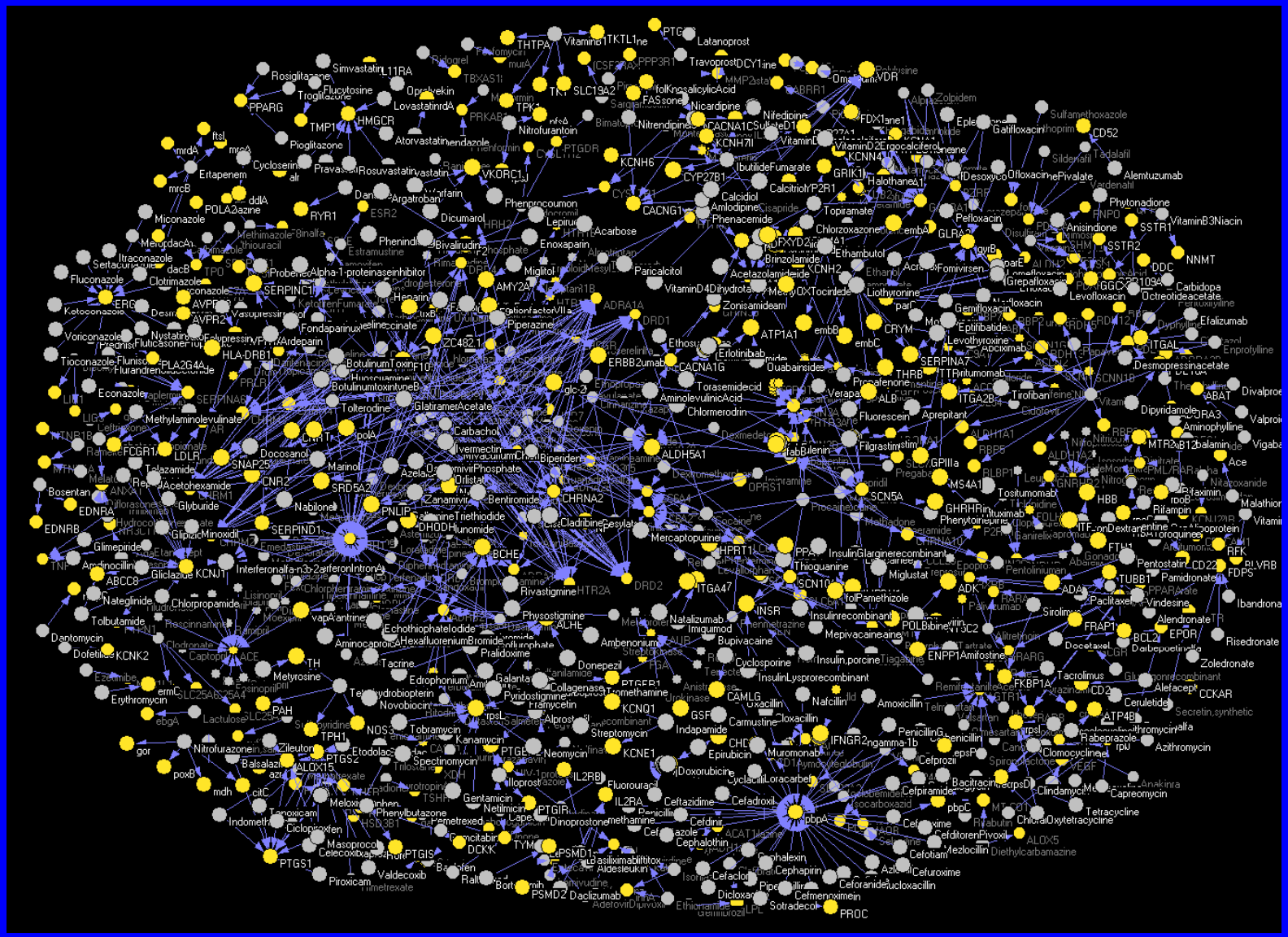
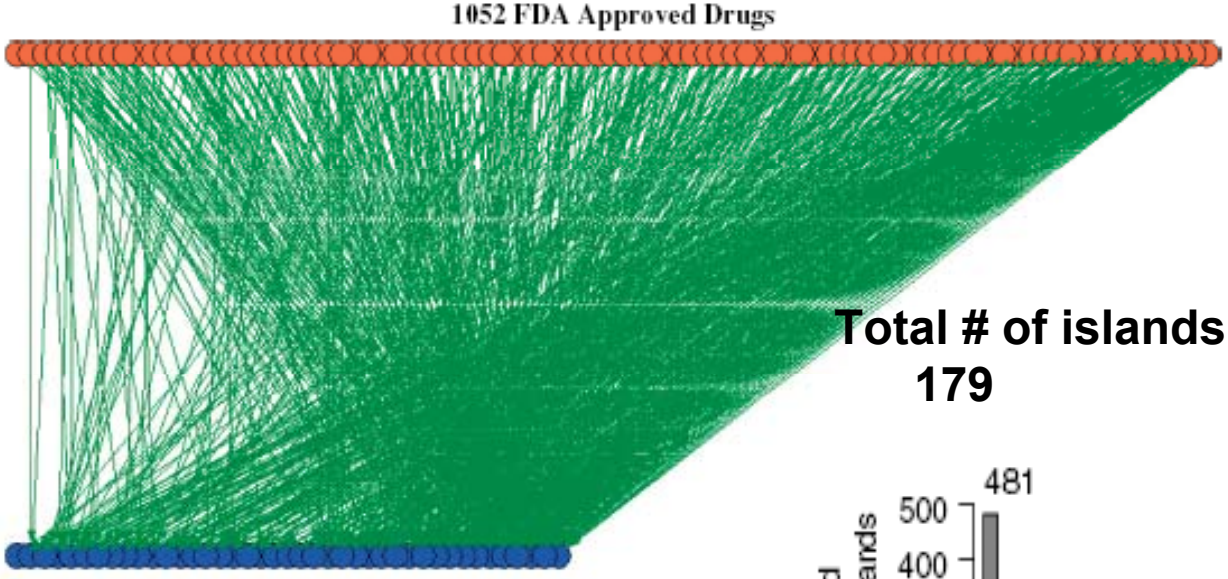
NEW YORK

Nature Precedings : doi:10.1038/npre.2008.1749.1 : Posted 1 Apr 2008

Network Diagram of FDA Approved Drugs and their Targets (Human Gene Products)

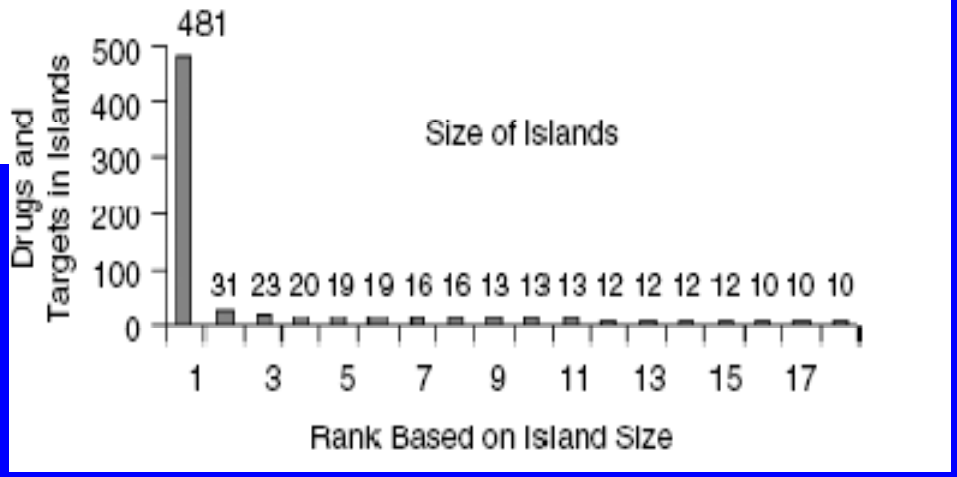


Systems Pharmacology: Global Relationship Between Therapeutic Drugs and the Human Genome



Drugs and their targets as a bipartite graph

Total # of islands 179



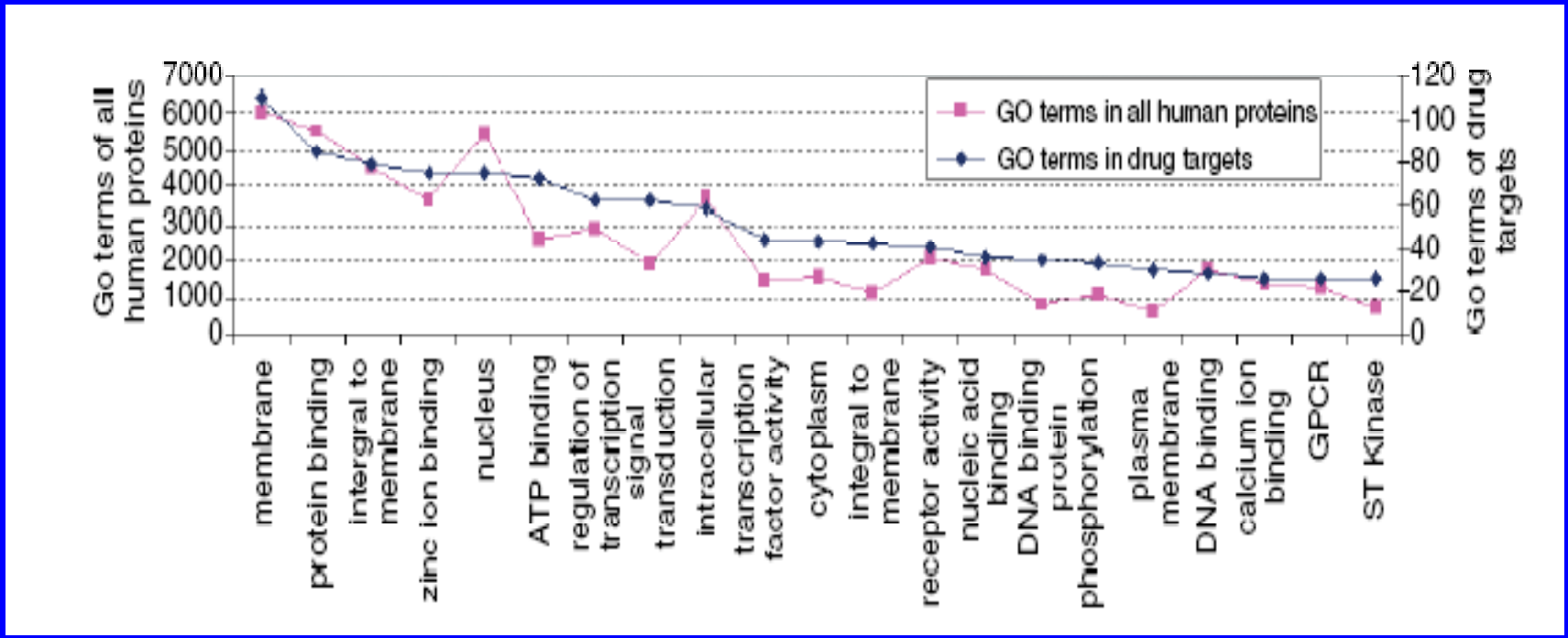
Many drug targets are part of networks, large and small

Each island is a network of interacting proteins

Avi Ma'ayan and Sherry Jenkins

Ma'ayan, Jenkins, Goldfarb, and Iyengar
Mount Sinai Journal of Medicine (2007) 74: 27-32

Functional annotation of human drug targets



GO Gene Ontology

Validates our assumption that current drug targets are signaling proteins

Ma'ayan, Jenkins, Goldfarb, and Iyengar
Mount Sinai Journal of Medicine (2007) 74: 27-32

Relationship between Adverse Effects and the Human Genome

Table 1. Active ingredients can cause adverse effects through 12 different scenarios. The precursor, the active drug, or drug metabolites resulting from chemical processing of the drug, can interact with the intended target but cause the target to initiate undesired effects (scenarios 1, 5 and 9). The three possible different forms of the drug can interact with other unknown or undesired targets in the same cell type (scenarios 2, 6 and 10) or different cell types (scenarios 4, 8 and 12). Also, the three possible different forms of the drugs can cause unwanted effects by targeting the intended target but in the unintended cell type (scenarios 3, 7 and 11).

	Same cell same target	Same cell different target	Different cell same target	Different cell different target
Drug precursor	Scenario 1	Scenario 2	Scenario 3	Scenario 4
Active drug	Scenario 5	Scenario 6	Scenario 7	Scenario 8
Drug metabolites	Scenario 9	Scenario 10	Scenario 11	Scenario 12

There are likely to be multiple mechanisms underlying adverse effects

Ma'ayan, Jenkins, Goldfarb, and Iyengar
Mount Sinai Journal of Medicine (2007) 74: 27-32

Systems Pharmacology

Some questions Systems Pharmacology can tackle

How do we go from such general analysis to specific situations ?

After all drugs are designed to treat specific pathophysiologies by interacting with specific targets !

Can network analysis be used to understand complex diseases and adverse events by drugs that are currently being used?

Systems Pharmacology Approaches

Build cellular networks using disease gene products as starting points.

Identify boundaries of functional neighborhoods (i.e. cellular interaction networks) of products of disease genes.

Do targets of drugs that cause the same clinical phenotype fall within the neighborhood ?

Seth Berger

What can we find using Systems Pharmacology Approaches?

Predictions for new susceptibility genes (mutations and SNPs) for disease origins as well as adverse effects

Ranked list of cellular components that upon interaction with drugs can cause clinical phenotype (generally adverse effects)

Systems Pharmacology of Arrhythmias

Long QT Syndrome

Prolonged QT Interval on EKG

Delayed repolarization after depolarization of cardiac ventricles

Syncope, Sudden death, Ventricular arrhythmias, Torsades de Pointes

Congenital

10+ genes with known causative mutations

Cardiac ion channels and related proteins

Acquired

Metabolic disturbances

Drug-induced

Many thanks to
Dan Roden
Vanderbilt

Drug Induced LQTS

- More than 70 FDA approved drugs
  - Spanning several classes
  - Direct HERG ion channel blockade
    - Most common
    - Degree of blockade is not directly related to risk of arrhythmia
  - Channel trafficking
  - Signal crosstalk
  - Reduced repolarization reserve

Susceptibility and risk modifier genes for drug induced LQTS

Identifying the Disease Gene Neighborhood

Develop an Integrated Mammalian Protein-Protein Interaction (PPI) Database

Consolidated 9 publicly available protein-protein interaction databases

Biogrid, HPRD, MINT, PDZbase, Reactome, DIP, Intact, Mips, PhosphoELM

Used gene orthology (Jackson Labs and NCBI homologene) to merge non-human mammalian proteins and their human orthologs

Resulting Network contains:

10,351 nodes (gene products)

64,411 edges (interactions)

19,810 references

Identifying the Disease Gene Neighborhood

Identify Functional Node Distance

Usually Shortest Path

Bias for hubs (nodes with many connections)

We have used mean first passage time (MFPT)
To measure functional distance from the disease gene

Distance in a PPI network has been used to:

Identify functional modules

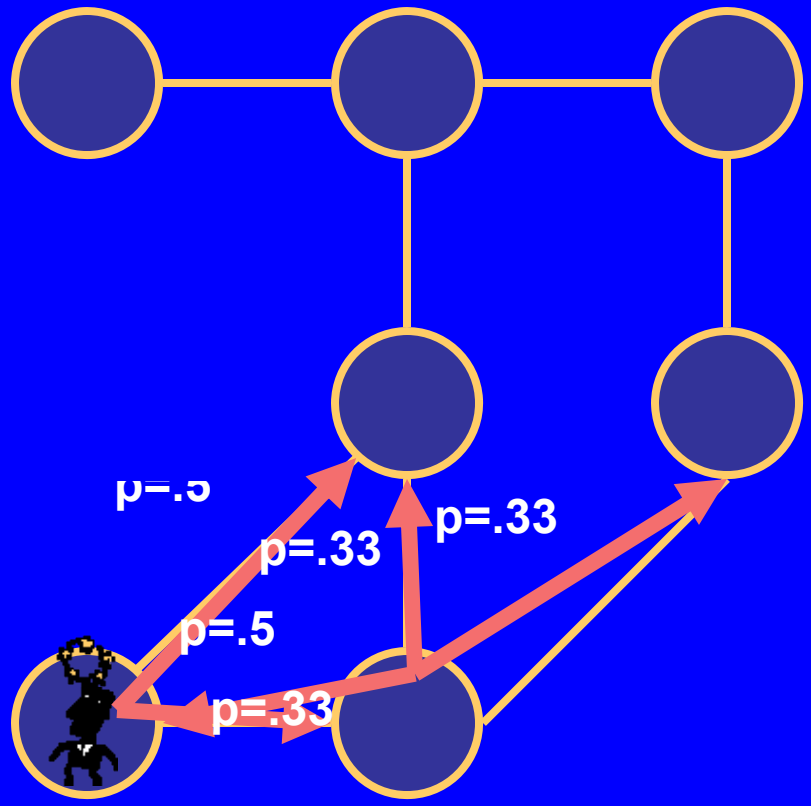
Annotate proteins with Gene Ontology Terms

Identify disease gene candidates

Calculating "Functional Distance" Between Nodes Using Random Walks

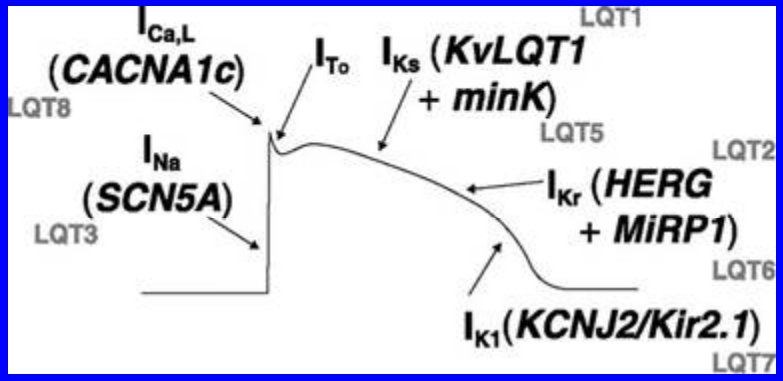
A random walker can step from any node to any adjacent node with equal probability.

Mean First Passage Time describes number of steps on average it takes a random walker to walk from a specified node to another specified node.



Long QT Syndrome Disease Gene List

- 10 genes with known causative mutations
  - Different mutations in some of same genes cause Short QT syndrome
- 1 gene (ALG10) annotated at as Reduced Susceptibility to LQTS
- Mostly Cardiac Ion Channels and related Proteins



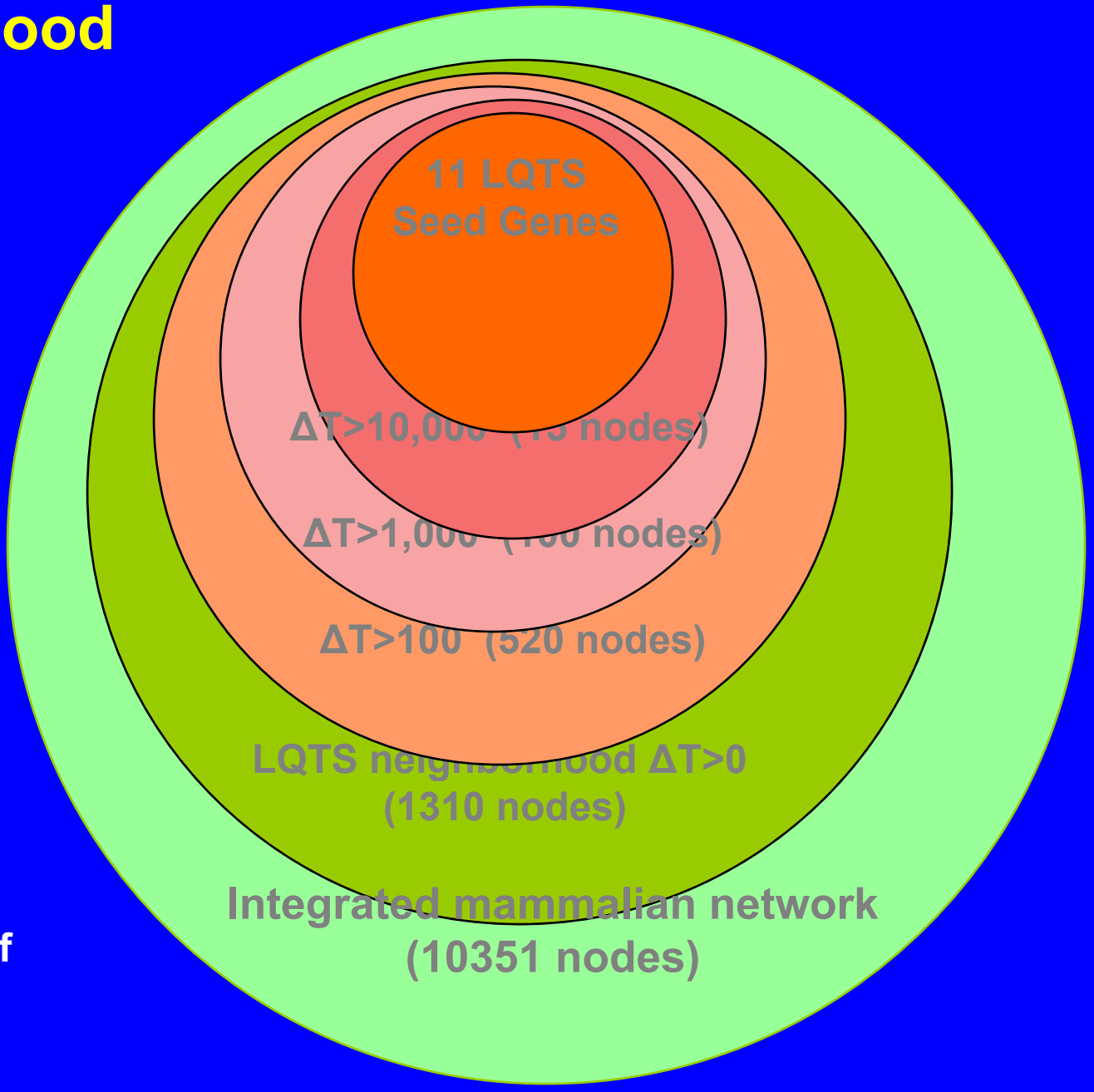
HERG = KCNH2 + MIRP = KNCE2

KvLQT1 = KCNQ1 + minK = KCNE1

KCNQ1 (3784)	potassium voltage-gated channel, KQT-like subfamily, member 1
KCNH2 (3757)	potassium voltage-gated channel, subfamily H (eag-related), member 2
SCN5A (6331)	sodium channel, voltage-gated, type V, alpha subunit
ANK2 (287)	ANK2 ankyrin 2, neuronal
KCNE1 (3753)	potassium voltage-gated channel, Isk-related family, member 1
KCNE2 (9992)	potassium voltage-gated channel, Isk-related family, member 2
KCNJ2 (3759)	potassium inwardly-rectifying channel, subfamily J, member 2
CACNA1 C (775)	calcium channel, voltage-dependent, L type, alpha 1C subunit
CAV3 (859)	caveolin 3
SCN4B (6330)	SCN4B sodium channel, voltage-gated, type IV, beta

LQTS Neighborhood

Statistical cutoffs from MFPT analysis to define boundaries of the LQTS neighborhood



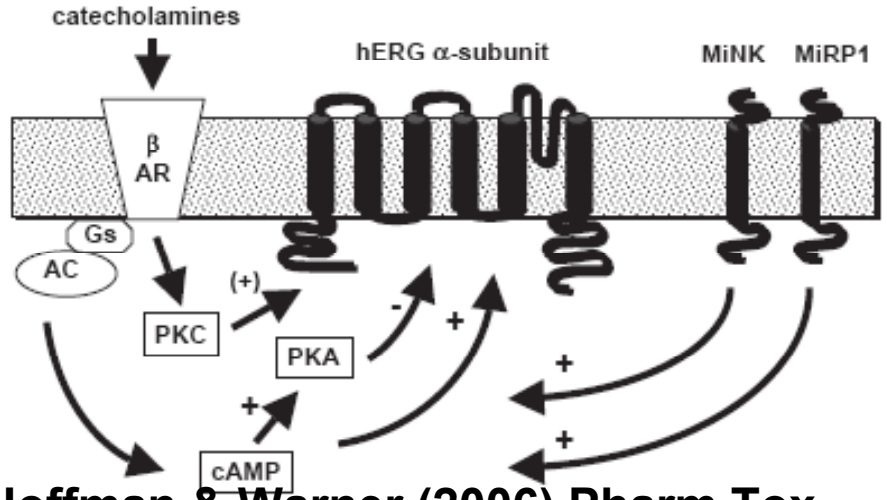
Even the biggest neighborhood has only 12.5% of the total nodes

Top 50 Ranked Nodes in the neighborhood

41 Nodes are 1-3 hops from Disease Genes

These include PKA and PKC

(See figure) And AKAP 9

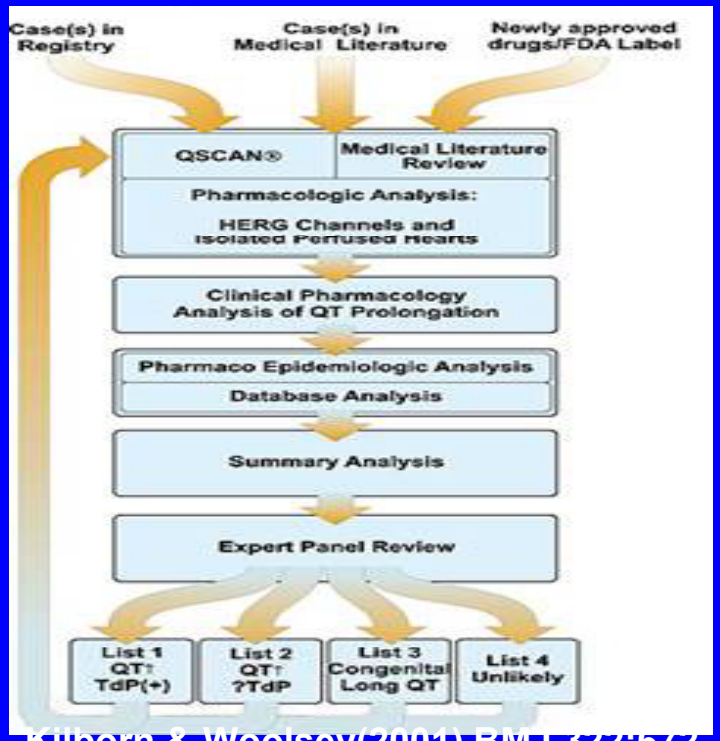


Hoffman & Warner (2006) Pharm Tox Meth 53:87

Drug Targets

Do drugs which show qt prolongation as a side effect or LQTS and Torsades De Pointes as adverse events have targets that are within the LQTS-Neighborhood?

ArizonaCERT qtdrugs database



Kilborn & Woolsey(2001) BMJ 322:672

DrugBank database

Wishart DS et al Nucleic Acid Res (2006) 34: D668-D672

LQTS Disease Gene Products Targeted by Drugs

Rank	Node	Score	Drug
1	KCNH2	50904	ibutilide_fumarate; propafenone
2	KCNQ1	34145.7	indapamide
5	KCNE1	23693.8	indapamide
10	KCNJ2	13781.3	levosimendan
11	CACNA1C	13560.9	magnesium_sulfate; ibutilide_fumarate; nicardipine
14	SCN5A	12792.7	quinidine; lamotrigine; indecainide; cocaine; benzonatate; encainide; tocainide; propafenone; disopyramide; riluzole; mephenytoin; mexiletine; procainamide; moricizine; bepridil; gabapentin; verapamil; hexylcaine; lidocaine; carbamazepine; flecainide; dibucaine; oxcarbazepine; phenytoin; prilocaine; ethotoin

qt drug from Arizona CERT; qt prolonging or torsadogenic from pubmed search; not in Arizona CERT list or found by pubmed search. Treatment for TdP

Top Network Analysis Identified Drug Targets

10 nodes in the networks with ranks from 43-84 show relevance to QT effect

Some nodes are disease genes for other diseases that also show QT prolongation as a associated pathophysiology

Some nodes are targets for drugs on ArizonaCERT QT drug base

Initial Findings

MFPT Ranking provides a continuum of scores, emphasizing "more specific interactors" as compared to highly connected hubs.

Known modulators of Torsadagenesis ranked highly

- Protein kinase C ranks 15
- Protein kinase A ranks 20.
- **AKAP9** ranks 19 ** Recently found mutation linked to LQTS! **
- **ADRA1D** and **ADRB1** and **ADRB2** rank within top half of the neighborhood
- **NOS1AP** (nitric oxide synthase 1 [neuronal] adaptor protein) , a known modulator of QT interval, is ranked 367.

Initial Findings → Conclusions

Targets of drugs that are associated with acquired LQTS are closer to the LQTS disease genes by 2:1 as compared to targets of drugs in general

This suggests a region of protein-protein interaction space which, when targeted pharmaceutically, is more likely to cause QT interval prolongation or Torsade de Points.

Such a ranked list of genes can be used to screen for LQTS susceptibility polymorphisms in further studies.

*New drug candidates can be screened for interactions with proteins in the list. Interactions may **suggest** that drug could have LQTS as an adverse effect*

Initial Findings → Conclusions

Such a ranked list of genes can be used to screen for LQTS susceptibility polymorphisms in further studies.

Are the gene products found in myocytes ?

*New drug candidates can be screened for interactions with proteins in the list. Interactions may **suggest** that drug could have LQTS as an adverse effect*

Cell type and tissue type specification of gene products and cell type specific networks